

Outcomes following early parenteral nutrition use in very preterm neonates

Version 1.0
Date: 20/06/2018

SPONSOR: Imperial College London

FUNDER: Access to the NNRD through unrestricted funds awarded to Prof N Modi. Data analysis funded within a Mason Medical Research Foundation fellowship awarded to Dr J Webbe.

STUDY CO-ORDINATION: Section of Neonatal Medicine, Imperial College London, Chelsea and Westminster Hospital campus

HRA REC Approval: 238670

Study Group

Chief Investigator: Dr Christopher Gale

Co-investigators: Dr James Webbe, Dr Sabita Uthaya, Professor Neena Modi

Statistician: Dr Nicholas Longford

Data analyst: Kayleigh Ougham

Parent representatives: Laura Noakes, Angela Richard-Löndt

Sponsor

Imperial College London; for further information regarding sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary's Hospital
Praed Street
London
W2 1NY
Tel: 020759 41862

Should corrections or amendments be necessary to this protocol these will be circulated to all investigators. Queries relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

STUDY SUMMARY	5
PLAIN ENGLISH SUMMARY	6
1. INTRODUCTION	8
1.1 BACKGROUND	8
1.2 RATIONALE FOR CURRENT STUDY	8
2. STUDY OBJECTIVES	9
3. RESEARCH QUESTIONS	9
4. STUDY DESIGN	10
4.1 STUDY OUTCOME MEASURES	10
5. PARTICIPANT ENTRY	11
5.1 INCLUSION CRITERIA	11
5.2 EXCLUSION CRITERIA	11
5.1 STUDY FLOW CHART	11
6. STATISTICS AND DATA ANALYSIS	12
6.1 BACKGROUND VARIABLES TO BE USED FOR MATCHING	12
6.2 STATISTICAL ANALYSIS	14
6.3 SUBGROUP ANALYSIS	14
6.4 SAMPLE SIZE CALCULATION	14
7. REGULATORY ISSUES	15
7.1 ETHICS APPROVAL	15
7.2 CONSENT	15
7.3 DATA PROTECTION AND CONFIDENTIALITY	15
7.4 INDEMNITY	15
7.5 SPONSOR	15
7.6 FUNDING	15
8. STUDY MANAGEMENT	15
9. PUBLICATION POLICY	16
10. REFERENCES	17

GLOSSARY OF ABBREVIATIONS

HRA	Health Research Authority
ICU	Intensive care unit
MRC	Medical Research Council
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NNAP	National Neonatal Audit Project
NNRD	National Neonatal Research Database
NDAU	Neonatal Data Analysis Unit
NICU	Neonatal Intensive Care Unit
PICU	Paediatric Intensive Care Unit
PN	Parenteral nutrition

STUDY SUMMARY

TITLE Outcomes following early parenteral nutrition (PN) use in very preterm neonates

DESIGN Two components:
A) Epidemiological survey of practice
B) Retrospective cohort study.

AIMS A) To describe early PN use in neonatal units in England, Wales and Scotland.

B) To identify whether the use of PN in the first seven postnatal days affects survival in neonates born between 30 and 33 weeks postmenstrual age.

To explore how PN use in the first seven postnatal days affects other important neonatal outcomes in neonates born between 30 and 33 weeks postmenstrual age.

OUTCOME MEASURES A) Use of any PN during the first seven postnatal days.
B) Primary outcomes: Survival to hospital discharge.
Secondary outcomes: Sepsis, necrotising enterocolitis, brain injury, retinopathy of prematurity, need for surgical operation, seizures, growth, bronchopulmonary dysplasia, blindness, deafness and ability to walk.

POPULATION A) All neonates born in England, Wales and Scotland and admitted to a NHS neonatal unit over the period 1st January 2008 to 31st December 2017.

B) All neonates born between 30 and 33 weeks^{+days} postmenstrual age in England, Wales and Scotland and admitted to a NHS neonatal unit between 1st January 2012 and 31st December 2017.

ELIGIBILITY A) All neonates admitted to a NHS neonatal unit (born between 23 and 42 weeks postmenstrual age).

B) Neonates born between 30 and 33 weeks^{+days} postmenstrual age who received PN in the first seven postnatal days.

COMPARATORS A) No comparator group; descriptive study.

B) Neonates born between 30⁺⁰ and 33 weeks^{+days} postmenstrual age who received no PN in the first seven postnatal days.

DATA SOURCE De-identified data held in the National Neonatal Research Database (NNRD) will be used.

KEYWORDS

Parenteral nutrition, preterm, neonate, core outcomes set, NNRD, propensity score, neonatal care

PLAIN ENGLISH SUMMARY

BACKGROUND

Each year in the UK about 60,000 babies are born too early (before they have reached 37 weeks of pregnancy). Most premature babies need specialist care and often spend weeks or even months on a neonatal unit.

An essential part of neonatal care is providing nutrition to ensure that babies grow and develop. Providing this can be difficult in premature babies because their intestines and other organs are underdeveloped. They often have difficulty digesting milk. Milk feeds are therefore introduced gradually. To help babies grow and develop during this period, additional nutrition may be provided as a fluid into a vein; this is called “parenteral nutrition” (PN). Unfortunately, PN increases the risk of serious complications like bloodstream infection (also known as “sepsis”).

There is general agreement that the benefits of PN outweigh the risks in babies who are extremely premature, i.e. those born more than 12 weeks early. Babies born near term have adequate fat reserves and so are unlikely to benefit from PN. For babies who are moderately premature there is little evidence to guide decision making about which babies will benefit from PN. This group of babies have more reserves of fat and are less dependent on PN, but are still at risk of sepsis. This means the risks and benefits of PN are less clear. As a consequence, some doctors use PN and others do not. The number of babies receiving PN across England, Scotland and Wales is unknown.

AIMS

Firstly, to describe which babies are given PN during the first postnatal week in neonatal units in England, Scotland and Wales.

Secondly, to determine whether in babies born 7-10 weeks preterm (moderately premature), providing PN in the first week after birth, compared to not to providing PN, improves survival to discharge from the neonatal unit.

Finally, to evaluate if the early use of PN in moderately preterm babies affects other important outcomes identified in related research called “Core Outcomes in Neonatology” where James Webbe obtained the views of over 250 former neonatal patients and parents (along with 150 nurses, doctors and researchers) to identify which outcomes they want neonatal research to focus on.

IMPORTANCE

This work will describe the extent of PN use in England, Scotland and Wales. This is currently unknown. This project will improve understanding of the balance of benefits and harms of PN use in premature babies and will help doctors and parents make informed treatment choices. My results will also inform future research to identify the best nutritional management for premature babies.

METHODS

James Webbe will use the National Neonatal Research Database (NNRD) to study all babies born in England, Scotland and Wales that received NHS neonatal care over the period 2008-2017. James Webbe will identify which babies were given PN during the first week, and which were not.

James Webbe will use the NNRD to identify babies born 7-10 weeks prematurely. James Webbe will compare outcomes in babies that were given and not given PN in the first week after birth.

The NNRD stores information from the electronic patient records (the computerised medical notes) of all babies born in England, Wales and Scotland who are admitted to a neonatal unit. All information held in the NNRD has had any identifying details removed, so no baby can be identified. James Webbe and Nick Longford will use statistical techniques to identify two sets of babies in the NNRD who are very similar (in terms of how prematurely they were born, their birth weight, sex, illness, and so on) with the only difference being in whether they were given PN or not. Neonatal Data Analysis Unit staff will then extract data from the NNRD about the outcomes (such as survival) and will compare the groups to see if there are any differences. As the two groups will be similar any difference in their outcomes is likely to be due to whether or not they received PN.

BENEFITS

The results of this research will help doctors make decisions and guide practice in an area in which there is currently very little evidence. This work will provide more information about the balance of risks to benefits of PN use in premature babies. The results of this work will also inform future research to identify how best to ensure babies receive the nutrition they need.

1. INTRODUCTION

1.1 BACKGROUND

Premature birth abruptly ends the transplacental transmission of nutrients that allows normal foetal growth and development. Providing adequate nutrition is essential to allow premature babies to continue to grow and mature. Very preterm infants often have difficulty tolerating adequate volumes of milk feeds shortly after birth due to the impaired mechanical and digestive function of their immature gut (1). To meet their nutritional needs they are given supplemental parenteral nutrition (PN). Preterm babies are among the highest PN users of all NHS patients. In some units it has been estimated that PN is received by around 70% of neonatal admissions (2). However, how PN affects outcomes has never been tested in a large scale, randomized, placebo controlled neonatal trial.

It is known that PN carries well established risks, of which the most serious and the most common is sepsis (3) with estimates of risk ratios varying from 2.2 to 14.6. In addition there is a growing body of evidence that use of PN within the first seven days of admission to an intensive care unit is associated with worse outcomes in critically unwell adults (4) and children (5). A subgroup analysis of the paediatric intensive care unit population focusing on neonates showed an increase in infections with early PN use (5). This suggests that uncertainty exists over the benefit of giving neonates PN in the early postnatal period. It is generally accepted that PN is beneficial to extremely preterm neonates, but in moderately preterm neonates the effect that PN use has on neonatal survival or other key outcomes has never been conclusively demonstrated (6-8).

The uncertainty over how PN use affects neonatal outcomes is reflected by the wide variation in how PN is used in different units, where differences in use, timing and composition of PN (9, 10) are seen. This is, in part, due to the lack of clear evidence of how PN affects neonatal outcomes like growth and survival. Neonates are also vulnerable to unanticipated treatment effects across different organ systems (11), therefore it is important to show that PN, like other therapies, does not adversely impact any important neonatal outcomes.

1.2 RATIONALE FOR CURRENT STUDY

The postmenstrual age at which the nutritional benefits of PN outweigh the risks in moderately preterm babies (30-33 weeks postmenstrual age) is unknown. It is therefore unsurprising that their nutritional management is very variable (9, 12-14). In moderately preterm neonates in 2012 and 2013 across England, Scotland and Wales PN was given to 45% of neonates, suggesting clinician equipoise around the balance of benefit to risk.

Identifying whether moderately preterm neonates benefit from PN would have important implications for practice in the UK, and will provide information to guide practice and inform future research.

2. STUDY OBJECTIVES

- To describe the use of PN in neonatal units across England, Scotland and Wales.
- To identify if use of PN in the first seven postnatal days affects survival in neonates born between 30 and 33 weeks postmenstrual age.
- To explore how PN use in the first seven postnatal days affects other important neonatal outcomes in neonates born between 30 and 33 weeks postmenstrual age.

3. RESEARCH QUESTIONS

A:

Which neonates receive PN during the first postnatal week in neonatal units in England, Scotland and Wales?

B:

In preterm neonates born between 30 and 33 weeks postmenstrual age (Population) does administration of PN in the first seven postnatal days (Intervention) compared with no PN (Comparator) improve survival to discharge home (primary Outcome)?

In preterm neonates born between 30 and 33 weeks postmenstrual age (Population) does administration of PN in the first seven postnatal days (Intervention) compared with no PN (Comparator) improve the outcomes in the core outcomes set for neonatology (secondary Outcomes)?

4. STUDY DESIGN

A: an epidemiological survey of practice using the National Neonatal Research Database (NNRD).

B: a retrospective cohort study of matched groups of babies using data held in the NNRD.

4.1 STUDY OUTCOME MEASURES

A: Primary outcome: any use of PN in the first seven postnatal days.

B: Primary outcome: Survival to discharge home; defined as recorded as alive at final neonatal unit discharge.

Secondary outcomes: other components of the neonatal core outcomes set (15). These include short term outcomes during the neonatal unit admission:

- Late Onset Sepsis; defined in line with the Royal College of Paediatrics and Child Health National Neonatal Audit Programme (NNAP) definition “pure growth of a pathogen from blood” or “pure growth of a skin commensal” or a “mixed growth” after the first 72 hours of life (16)
- Necrotising enterocolitis; defined using the NNAP definition (16)
- Brain injury on imaging; defined as documented diagnosis of intraventricular haemorrhage (grade 3-4) (17) or cystic periventricular leucomalacia
- Retinopathy of prematurity; defined as a record of any retinopathy of prematurity on routine screening in the National Neonatal Dataset “retinopathy of prematurity ad-hoc form”
- Bronchopulmonary dysplasia; defined using the NNAP definition (16) of significant bronchopulmonary dysplasia.
- Need for surgical procedures; defined as any record of surgical procedure during the neonatal admission
- Seizures; defined as any recorded diagnosis of seizures or seizure disorder
- Growth; weight and head circumference at discharge; weight velocity and head circumference velocity from birth to discharge

Long term outcomes after discharge will also be measured:

- Blindness; defined as an answer of Yes to the question “Does this child have a hearing impairment?” on the NNAP form (16)
- Deafness; defined as an answer of Yes to the question “Does this child have a hearing impairment?” on the NNAP form (16)
- Ability to walk; defined as an answer of Yes to the question “Is this child unable to walk without assistance?” on the NNAP form (16)

It will not be possible to measure the following components of the core outcomes set: quality of life, gross motor ability or cognitive ability as relevant data are not captured in the NNRD.

5. PARTICIPANT ENTRY

5.1 INCLUSION CRITERIA

A: Neonates born between 1st January 2008 and 31st December 2017 and admitted to a neonatal unit in England, Scotland and Wales).

B: Neonates born between 30 and 33 weeks postmenstrual age between 1st January 2012 and 31st December 2017 and admitted to a neonatal unit in England, Scotland and Wales).

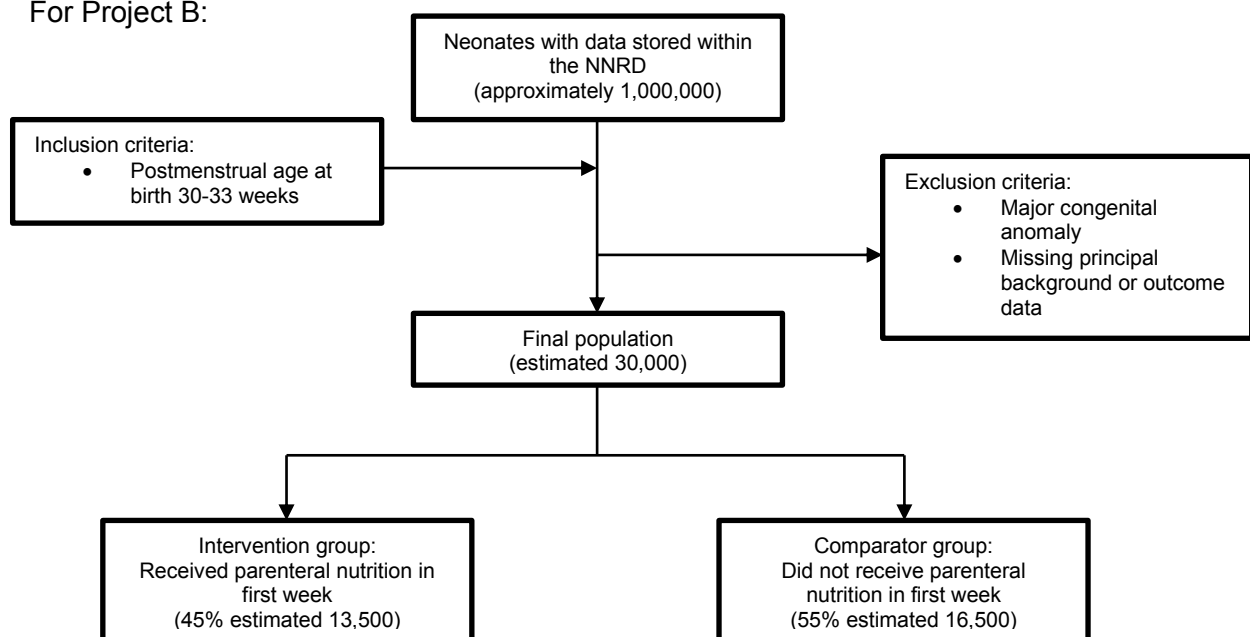
5.2 EXCLUSION CRITERIA

A: No exclusions.

B: Neonates with major congenital gastrointestinal malformations will be excluded as they cannot be fed enterally. Neonates with life limiting conditions or conditions requiring surgery in the neonatal period will be excluded from the analysis as they will not receive standard neonatal nutritional care. Neonates with missing key background data (birthweight, sex or gestational age) or data for the primary outcome will be excluded.

5.3 STUDY FLOW CHART

For Project B:



6. DATA ANALYSIS

A: James Webbe will extract data to identify the characteristics of neonates who receive PN in the first seven postnatal days. Parenteral nutrition use will be described by gestational age, birth weight, over time and by geographical region.

B: James Webbe and Nick Longford will use propensity matching within the potential outcomes framework to minimise bias and confounding. James Webbe and Nick Longford will ensure the two groups are as similar as possible (with the exception of the intervention; exposure to PN in the first week) by generating two matched cohorts for comparison.

6.1 BACKGROUND VARIABLES TO BE USED FOR MATCHING

A: No matching necessary.

B: Neonates will be matched on postmenstrual age at birth and low birth weight. Postmenstrual age will be matched by week. Low birth weight will be treated as a dichotomous variable, with the threshold being the 10th centile for weight on the UK-WHO growth chart (18). These factors are likely to significantly affect both the decision to administer PN and eventual outcomes and so are potential sources of bias requiring additional matching.

For postmenstrual age at birth neonates will be matched only with neonates born in the same postmenstrual week (i.e. a neonate born at 30+2 will be matched with a neonate born between 30+0 and 30+6). For low birth weight neonates will be matched according to whether their weight at birth falls below the 9th centile for their sex and postmenstrual age (using WHO growth charts).

In addition propensity score matching will be used for the following variables:

- Demographic data items
 - Sex
 - Multiplicity
 - Year of birth
- Maternal factors
 - Age
 - Gestational diabetes
 - Severe pre-eclampsia requiring pre-term birth
 - Severe pre-eclampsia
 - Gestational hypertension
 - Prolonged rupture of membranes (>24 hours)
 - Suspected chorioamnionitis
 - Receipt of antenatal steroids
 - Receipt of antenatal magnesium sulphate
- Infant factors: Birth and Resuscitation
 - Apgar score at 5 minutes

- Chest compressions administered
- Emergency resuscitation drugs administered
- Intubated at resuscitation
- Umbilical cord pH
- Surfactant administered
- Infant factors: condition on neonatal unit and initial treatment
 - Admission temperature
 - Admission mean blood pressure
 - Admission blood glucose
 - Admission heart rate
 - Admission oxygen saturation
- Infant factors: first day care
 - Surfactant administered
 - Mechanical ventilation on Day 1
 - Inotropes administered on Day 1
 - Sepsis suspected on Day 1
 - Transfer on Day 1
- Organisational factors
 - Level of initial neonatal unit
 - Neonatal network

Factors occurring on the first day of admission to the neonatal unit will be matched as they will be independent of the administration of PN and will help to ensure the two cohorts are balanced. Factors occurring after the first day of admission will not be matched as they will not be independent of the administration of PN.

Propensity score matching will allow causal inferences to be made from observational data by balancing potentially confounding factors (19). Due to the large number of factors that need to be balanced the use of propensity score matching will allow matching to occur without the loss of a large number of observations. Using the large population size and wide range of background data available in the NNRD will allow us to achieve well balanced cohorts; this will enhance the credibility of analysis.

Cohorts balanced on all the background variables are formed by the following process. Propensity scores (the probability of being assigned PN based on background variables) will be calculated using a logistic regression model. Matched pairs (where one individual received PN and one did not) will be identified with similar propensity scores. These matched pairs then form the two cohorts: treated with PN within the first week or not treated. The balance on all background variables between these cohorts is assessed using a balance plot. The logistic regression model is then refined (for example by the addition of further variables) and a new balance plot constructed. This process is repeated until no further improvement in balance can be achieved. This ensures that the propensity scores have been adequately specified to identify balanced groups (20).

6.2 STATISTICAL ANALYSIS

A: Rates of early PN use will be calculated from population level data. James Webbe will compare PN use in neonates born at different postmenstrual ages and different birth weights (using the WHO classification) (21). Rates of PN use will be compared between different groups using the Chi-squared test.

B: Absolute risk differences and odds ratios for the pre-specified, dichotomous outcomes will be calculated. All p values calculated will be two-sided. When analysing the secondary outcomes due to the risk of multiple comparisons to avoid erroneous inferences the Holm-Bonferroni method (22) will be used.

6.3 SUBGROUP ANALYSES

A: James Webbe will compare PN use at neonatal network level. James Webbe will also compare how PN use has changed over the 5 year period in the different gestational age and birthweight groups using analysis of variance testing.

B: James Webbe will undertake a planned sensitivity analysis to explore the possibility that a missing binary variable explains the effect size seen. James Webbe will construct a dichotomous variable intended to stack the odds against the superior treatment option and then compare this to the background variables to explore whether it is plausible that such a “missing” variable exists.

6.4 SAMPLE SIZE

A: Around 90,000 neonates are admitted to neonatal units in England, Scotland and Wales each year. Since 2008 the NNRD holds data on approximately 1,000,000 babies.

B: James Webbe has calculated that 12,000 neonates are required in each group (*PN* and *No PN*) in order to have 90% power to detect (with two-sided significance of 5%) an absolute difference in survival to discharge of 1.3% between the two groups. Pilot data suggests that over the five year period James Webbe will have 13,500 neonates in the *PN* group and 16,500 in the *No PN* group.

The absolute difference expected is calculated using the mortality rate of 3.4% for this group (23) and the odds ratio of 0.73 for early vs. late PN suggested by previous research (5). Pilot data suggests around 6,000 neonates each year are born between 30 weeks and 33 weeks postmenstrual age.

7. REGULATORY ISSUES

7.1 RESEARCH ETHICS APPROVAL

The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee approval (16/LO/1093), and Confidential Advisory Group approval (ECC 8-05(f/2010)), to form the NNRD. James Webbe will seek stand alone approval from the national research ethics service for this project. As this study has no material ethical issues with minimal risk, burden or intrusion for research participants James Webbe will seek proportionate review. The Chief Investigator has obtained approval from the HRA. The Chief Investigator will require a copy of the Trust Capacity and Capability approval email before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 CONSENT

No patient consent is required as only de-identified data from the NNRD will be used.

7.3 DATA PROTECTION AND CONFIDENTIALITY

All investigators and study site staff will comply with the requirements of the Data Protection Act and the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles. Only de-identified data will be used in this study. Imperial College will collect information for this research study from the Neonatal Data Analysis Unit. The Neonatal Data Analysis Unit will not provide any identifying information to Imperial College. We will use this information to complete the described research.

As no patient identifiable data will be used HRA Confidentiality Advisory Group approval is not required.

Data from the NNRD will be extracted by staff from the Neonatal Data Analysis Unit operating within the guidelines established by Research Ethics Committee approval (REC Reference: 16/LO/1093) and Confidentiality Advisory Group approval (CAG reference: ECC 8-05(f)2010). No member of the study team will have access to identifiable data on any study participant: they are not part of the clinical care team. Data for this work will be extracted from the NNRD. The NNRD is an established research database and holds National Research Ethics Service approval (16/LO/1093). Data held within the NNRD will be retained as a research database. A copy of the study data extract will be retained by the NNRD as part of the research database.

All data will be stored on a password secured computer in the Clinical Research Fellows' office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for 10 years in line with institutional policy.

7.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 SPONSOR

Imperial College London

7.6 FUNDING

The funding for creating and maintaining the NNRD is from unrestricted funding awarded to Prof Neena Modi. This funding includes costs involved in data transfer, storage, cleaning, merging, administration and regulatory approvals. The extraction of study data from the NNRD and analysis of data for this study is funded through a Mason Medical Research Fellowship awarded to Dr James Webbe.

7.7 DATA STORAGE

All data will be stored on a password secured computer in the Clinical Research Fellow's Office on the Chelsea and Westminster Hospital campus of Imperial College London. All data will be stored for ten years. All anonymised data can be accessed by contacting the primary investigator.

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Section of Neonatal Medicine at Imperial College London. Monitoring and auditing research conduct will be performed by the sponsor as required and according to the sponsor's standard operating procedure.

9. PUBLICATION POLICY

The results of this study will be reported as a manuscript in a peer-reviewed scientific journal. All members of the study group will be authors with additional contributors as appropriate. JW will be first author, CG will be last author.

10. REFERENCES

1. Fanaro S. Feeding intolerance in the preterm infant. *Early Hum Dev.* 2013;89:S13-S20.
2. Christensen RD, Henry E, Wiedmeier SE, Burnett J, Lambert DK. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. *Journal of perinatology : official journal of the California Perinatal Association.* 2007;27(5):284-90. Epub 2007/03/09.
3. Zingg W, Tomaske M, Martin M. Risk of parenteral nutrition in neonates--an overview. *Nutrients.* 2012;4(10):1490-503. Epub 2012/12/04.
4. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. *The New England journal of medicine.* 2011;365(6):506-17. Epub 2011/07/01.
5. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. *The New England journal of medicine.* 2016;374(12):1111-22. Epub 2016/03/16.
6. Heird WC, Gomez MR. Parenteral nutrition in low-birth-weight infants. *Annu Rev Nutr.* 1996;16:471-99.
7. Trivedi A, Sinn JKH. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. *Cochrane Db Syst Rev.* 2013(7).
8. Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. *The Cochrane database of systematic reviews.* 2005(2):CD005256. Epub 2005/04/23.
9. Lapillonne A, Kermorvant-Duchemin E. A systematic review of practice surveys on parenteral nutrition for preterm infants. *The Journal of nutrition.* 2013;143(12 Suppl):2061S-5S. Epub 2013/10/11.
10. Mason DG, Puntis JW, McCormick K, Smith N. Parenteral nutrition for neonates and children: a mixed bag. *Arch Dis Child.* 2011;96(3):209-10. Epub 2010/09/21.
11. Lanman JT, Guy LP, Dancis J. Retrolental fibroplasia and oxygen therapy. *Journal of the American Medical Association.* 1954;155(3):223-6. Epub 1954/05/15.
12. Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. *Clinics in perinatology.* 2002;29(2):225-44. Epub 2002/08/10.
13. Harding JE, Cormack BE, Alexander T, Alsweller JM, Bloomfield FH. Advances in nutrition of the newborn infant. *Lancet.* 2017;389(10079):1660-8. Epub 2017/04/27.
14. Lapillonne A, Carnielli VP, Embleton ND, Mihatsch W. Quality of newborn care: adherence to guidelines for parenteral nutrition in preterm infants in four European countries. *BMJ open.* 2013;3(9):e003478. Epub 2013/09/21.
15. Webbe J, Brunton G, Ali S, Duffy JM, Modi N, Gale C. Developing, implementing and disseminating a core outcome set for neonatal medicine. *BMJ Paediatrics Open.* 2017;1(1).
16. Royal College of Paediatrics and Child Health. National Neonatal Audit Programme A guide to the 2018 audit measures. Royal College of Paediatrics and Child Health, 2017.
17. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and Evolution of Subependymal and Intra-Ventricular Hemorrhage - Study of Infants with Birth Weights Less Than 1,500 Gm. *Journal of Pediatrics.* 1978;92(4):529-34.
18. Onis M, Onyango A, Borghi E, Siyam A, Pinol A, Garza C, et al. Enrolment and baseline characteristics in the WHO Multicentre Growth Reference Study. *Acta Paediatrica.* 2006;95:7-15.
19. Rosenbaum PR, Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika.* 1983;70(1):41-55.
20. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivar Behav Res.* 2011;46(3):399-424.

21. World Health Organization. International Statistical Classification of Diseases and Related Health Problems 10th Revision. 2016.
22. Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scand J Stat. 1979;6(2):65-70.
23. Manktelow BN, Smith LK, Prunet C, Smith PW, Bobby T, Hyman-Taylor P, et al. MBRRACE-UK Perinatal Surveillance Report: UK Perinatal Deaths for Births from January to December 2015. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester, 2017.